REMARKS

The present invention relates in part to methods for diagnosing stroke or cerebral injury in subjects. These methods comprise measuring at least the 108 amino acid BNP precursor or one or more of its related markers, and determining whether the marker(s) measured correlate to the occurrence or nonoccurrence of a stroke or cerebral injury.

Claims 32-41 are under examination. No amendments to these claims are presented herein. Applicants request reconsideration of the claimed invention in view of the following remarks.

1. 35 U.S.C. §103(a)

Applicants respectfully traverse the rejection of claims 32 and 37-41 under 35 U.S.C. § 103(a) as allegedly being obvious over Seilhamer *et al.*, U.S. Patent 6,897,030, in view of Nitta *et al., Am. J. Nephrol.* 18: 411-15, 1998, and in further view of Kelley *et al., Quart. J. Med.* 92: 295-97, 1999.

The claimed invention is drawn to a method of determining the occurrence or nonoccurrence of a stroke in a subject. In these methods, an assay is performed by contacting a sample of bodily fluid from the subject with an antibody that binds the 108 amino acid brain natriuretic peptide (BNP) precursor or one or more markers related thereto, such as BNP or NT-proBNP. The results of this assay are then used to determine the occurrence or nonoccurrence of a stroke in the subject.

The obviousness rejection is premised on the following assertions: (1) that Seilhamer *et al.* discloses immunoassays for detecting BNP, albeit not for determining the occurrence or nonoccurrence of a stroke; (2) that Nitta *et al.* discloses that BNP is elevated in certain patients with left ventricular dysfunction, a type of heart failure; and that (3) Kelley *et al.* discloses that asymptomatic left ventricular dysfunction may be found in some patients who have had a stroke.

Based on this, the Examiner asserts that it would have been obvious to use a BNP assay to evaluate stroke. Office Action, pages 4 and 5.

This, however, is a false conclusion to draw from the cited articles. The fact that BNP may be used to diagnose left ventricular dysfunction, and some stroke patients also have left ventricular dysfunction, does not lead to a conclusion that BNP may be used to diagnose stroke. Some stroke patients presumably also have diabetes, colon cancer, or twin siblings. Nothing in the cited articles, whether considered individually or together, leads to the conclusion that BNP can be used to diagnose any conditions other than left ventricular dysfunction, including the occurrence or nonoccurrence of stroke (or diabetes, colon cancer, or twin siblings).

It appears the Examiner concludes that the references somehow stand for BNP measurement for identifying LVSD. For example, the Examiner states, "[t]he measurement of BNP may reduce the number of patients needing echocardiograms, aide in identifying and treating LVSD to reduce the incidence of cardiac death." Office Action, page 5. However, this apparent conclusion is not supported by any scientific rational or legal underpinning to support the use of BNP as a marker to determine the occurrence or nonoccurrence of a stroke. Therefore, the Examiner has not elucidated any factual teachings, suggestions or incentives from this prior art that shows the propriety of the combination, nor in fact even point out what teachings from each of the references, when considered in combination, were relied upon in concluding that the claimed subject matter would have been obvious.

In view of the foregoing, Applicants respectfully submit that no *prima facie* case of obviousness has been established, and request that the rejection be reconsidered and withdrawn.

2. 35 U.S.C. §103(a)

Applicants respectfully traverse the rejection of claims 33 and 36 under 35 U.S.C. § 103(a) as allegedly being obvious over Seilhamer *et al.*, in view of Nitta *et al.*, in further view of Kelley *et al.*, and in further view of Jackowski *et al.*, WO00/52476.

The failure in establishing a *prima facie* case of obviousness with regard to Seilhamer *et al.*, Nitta *et al.*, and Kelley *et al.* are discussed above. And Jackowski *et al.* does not cure the flaws in the *prima facie* case. While Jackowski *et al.* is directed to methods for assessing stroke, Jackowski *et al.* does not teach or suggest the 108 amino acid brain natriuretic peptide (BNP)

precursor or one or more markers related thereto, such as BNP or NT-proBNP. Again, as discussed in Section 1 above, the Examiner has not elucidated any factual teachings, suggestions or incentives from this prior art.In view of the foregoing, Applicants respectfully submit that no *prima facie* case of obviousness has been established, and request that the rejection be reconsidered and withdrawn.

3. 35 U.S.C. §103(a)

Applicants respectfully traverse the rejection of claims 34 and 35 under 35 U.S.C. § 103(a) as allegedly being obvious over Seilhamer *et al.*, in view of Nitta *et al.*, in further view of Kelley *et al.*, and in further view of Velier *et al.*, *J. Neurosci.* 19: 5932-41, 1999.

The failure in establishing a *prima facie* case of obviousness with regard to Seilhamer *et al.*, Nitta *et al.*, and Kelley *et al.* are discussed above. In addition, Velier *et al.* does not cure the flaws in the *prima facie* case. Velier *et al.* does not teach or suggest the 108 amino acid brain natriuretic peptide (BNP) precursor or one or more markers related thereto, such as BNP or NT-proBNP as a possible marker in those methods. Instead, Velier *et al.* is directed to caspase-3 expression within the cerebral cortex following experimental cerebral ischemia following occlusion and transection by electrocoagulation of the middle cerebral artery.

Moreover, even as to caspase-3, the claimed subject matter relates to the measurement of caspase-3 in a bodily fluid sample from a subject. Velier *et al.* discloses that caspase-3 is expressed in brain tissue sections following this rather severe insult, but does not teach or suggest that caspase-3 would be measurable in body fluids, much less that its measurement in body fluids would be indicative for the occurrence or nonoccurrence of a stroke. The fact that caspase-3 is detectable in brain tissues indicates that it is sufficiently present therein, and that caspase-3 is not lost or entirely lost to bodily fluids.

In view of the foregoing, Applicants respectfully submit that no *prima facie* case of obviousness has been established, and request that the rejection be reconsidered and withdrawn.

4. Obviousness-type double patenting

With regard to the Examiner's provisional rejection for Obviousness-type double patenting, Applicants note that no terminal disclaimer is procedurally required in a case where the provisional rejection involves two pending applications and where the rejection is the sole remaining issue in the case. See MPEP 804 (I)(B) (The "provisional" double patenting rejection should continue to be made by the examiner in each application as long as there are conflicting claims in more than one application unless that "provisional" double patenting rejection is the only rejection remaining in at least one of the applications.") In the event that other rejections of the present claims are successfully overcome by the current communication, withdrawal of the instant provisional rejection would be appropriate. Applicants authorize the examiner to follow MPEP 804 (I)(B) and allow the case without issuing a further Office Action should the provisional obviousness type-double patenting rejection be the sole remaining issue in the case.

CONCLUSION

Applicants respectfully submit that the pending claims are in condition for allowance. An early notice to that effect is earnestly solicited. Should any matters remain outstanding, the Examiner is encouraged to contact the undersigned at the address and telephone number listed below so that they may be resolved without the need for additional action and response thereto.

FEE AUTHORIZATION

The Commissioner is authorized to charge any additional fees which may be required, including petition fees and extension of time fees, to Deposit Account No. **23-2415** (Docket No. 36671-743.503).

Respectfully submitted,

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